CHAPTER 3

MEDICAL
NUCLEAR, BIOLOGICAL, AND CHEMICAL WARFARE DEFENSE REQUIREMENTS AND RESEARCH AND DEVELOPMENT PROGRAM STATUS

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3.1 REQUIREMENTS

3.1.1 Introduction

The Gulf War, the Tokyo subway nerve gas (sarin) attack in March of 1995, the threatened release of radiocesium in Moscow's Izmailovo Park, and recently released reports[1, 2, 3] illustrate that many countries and terrorist groups have acquired the means for both producing chemical, biological and radiological weapons and delivering them. Nuclear, biological, and chemical (NBC) proliferation increases the threat to deployed U.S. forces. The May 1997 *Report of the Quadrennial Defense Review* (QDR) concluded that the threat or use of NBC weapons is a "likely condition of future warfare." In response, the mission of our medical chemical, biological, and radiological defense research program (MCBRDRP) is to preserve combat effectiveness by timely provision of medical countermeasures. The MCBRDRP has three goals:

(1) Provide individual level protection and prevention to preserve fighting strength;
(2) Maintain technological capabilities to meet present requirements and counter future threats; and
(3) Provide medical management of chemical, biological, and radiological weapons casualties to enhance survivability, and expedite and maximize return to duty.

Chemical warfare agents are available worldwide and include vesicants (blister agents), nerve, blood, and respiratory agents. Biological threat agents include bacteria, viruses, rickettsia and toxins, which can be produced by any group with access to a scientific laboratory or a pharmaceutical industry. The radiological threat is from the use of conventional explosives to spread nuclear contamination over a limited area or strategic terrain (including usage against reactors or industrial radiation sources) and potentially from the use of a single or a small number of crude, Hiroshima-type nuclear weapons. Exposure to multiple threats may result in synergistic effects. Medical treatment strategies reduce the performance decrement, injury, and death of military personnel in the field, thereby enabling them to accomplish their missions, as well as reducing the need for medical resources.

DoD medical NBC defense research and development has resulted in the fielding of numerous products to protect and treat service members against the effects of NBC weapons. The DoD program to stockpile biological defense products has been smaller than the chemical defense effort, but has received greater emphasis in recent years.

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1 Proliferation: Threat and Response, November 1997, DoD Report.

2 *Report to Congress on Response to Threats of Terrorist Use of Weapons of Mass Destruction*, January 31, 1997, prepared as requested by Public Law 104-201, National Defense Authorization Act for Fiscal Year 1997. SEC. 1411. Response to Threats of Terrorist use of Weapons of Mass Destruction.

3 *Report to Congress on Response to Threats of Terrorist Use of Weapons of Mass Destruction*, May 1, 1997. Prepared by the Department of Defense as requested by Public Law 104-201, National Defense Authorization Act for Fiscal Year 1997, Title XIV: Defense Against Weapons of Mass Destruction (WMD). Subtitle A: Domestic Preparedness.

Specific initiatives programmed to improve NBC medical readiness include:

- Continued emphasis on NBC medical countermeasures research.
- Medical collective protection.
- Identification and testing of medications and therapeutic regimens which reduce the effect of radiation on both bone marrow and the intestinal tract.
- A biological defense immunization policy.
- The award of a prime contract to develop, license, produce, and store biological defense vaccines.
- Enhanced medical diagnostic capability for disease caused by all agents.
- Definition of low dose radiation interaction on susceptibility to biological and chemical agents.

3.1.2 Challenges in the Medical NBC Warfare Defense Programs

Medical prophylaxes, pretreatments, and therapies are necessary to protect personnel from the toxic or lethal effects of exposure to all validated threat agents, as well as other anticipated threats. DoD has fielded a number of medical countermeasures, which greatly improve individual medical protection, treatment, and diagnoses.

DoD complies with all Food, Drug and Cosmetic Act requirements. The Food and Drug Administration (FDA) requires large-scale field trials in human subjects to demonstrate efficacy of drugs and biologicals prior to licensure. There are, however, legal and ethical constraints that preclude such efficacy studies for NBC countermeasures. While demonstration of a drug or vaccine's safety in humans is no different than any "civilian" pharmaceutical product, field studies of efficacy cannot be performed, since exposure to most NBC agents does not usually occur naturally. Moreover, the high lethality and/or toxicity of NBC agents makes it unethical to expose human subjects in the controlled efficacy studies usually required by the FDA for product licensure (*e.g.*, tests of effectiveness of the product against the threat in humans). DoD continues to work with the FDA to seek alternative methods for demonstrating efficacy of NBC medical countermeasures and to obtain their licensure. DoD has also begun the exploration of strategies with the FDA to address the challenges of using investigational products for force protection in deployment.

Contrary to many media reports[4], medical NBC defense products are thoroughly evaluated and tested for their safety in accordance with FDA guidelines (for example, see Figure 3-1 for biological products) before being administered to *any* personnel. All NBC defense medical products must be safe to use and not degrade operational performance. In cases where adverse effects are known or are possible, a decision must be made—and a risk accepted—of the real or potential effects of a medical product versus the catastrophic effects of unprotected exposure to NBC weapons. Even though efficacy may not be fully understood, safety (including

[4] See for example, Arthur Brice, "Sneaky use of drugs on GIs sparks debate," The Atlanta Journal-the Atlanta Constitution, December 4, 1997, p. D8.; Victor Sidel quoted in Dave Parks, "Military tries to plug chem defense gaps," *Birmingham News*, p.1; "Gulf War Syndrome," by Ed Bradley on *60 Minutes*, CBS-TV, September 29, 1996; "In general, a sickening syndrome," New York Daily News, December 7, 1996, p. 11; Thomas Tiedt quoted in David Ballingrud, "Ex-researcher: Gulf 'vaccine' was a poison," *St. Petersburg Times*, December 2, 1996, p. 1.

adverse effects) is understood extensively. In many cases, the safety is well understood because the medical products have been widely used to treat other medical conditions. (For example, pyridostigmine bromide, the investigational nerve agent pretreatment, has been in use since the 1950s to treat myasthenia gravis, a neuromuscular disorder. The anthrax vaccine is licensed and has been used since the 1970s to vaccinate veterinarians, textile workers, and others. Various anti-emetics to protect against radiological threats have been used to treat cancer patients undergoing radiation therapy.)

The acquisition life cycle of medical products developed by DoD is normally managed in accordance with the guidelines found in DoD Regulation DoD 5000.2-R. However, since DoD complies with FDA requirements, it must also follow the requirements of Title 21, Food & Drugs, Code of Federal Regulations (CFR). The following chart illustrates the correlation of events for each DoD 5000.2-R life cycle phase to the requirements of 21 CFR:

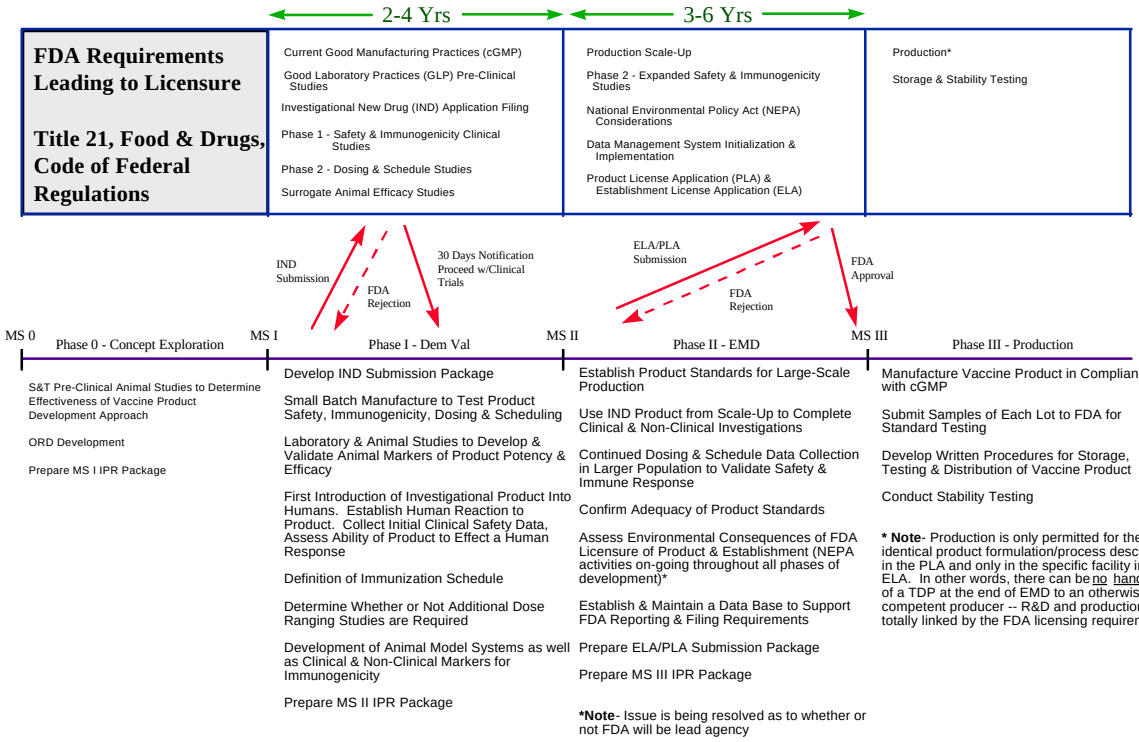

Figure 3-1. Standard FDA Approval Process for Biological Defense Medical Products

The medical NBC defense research programs discussed in this section are divided into three areas of research: chemical, biological, and nuclear. Table 3-3 (on page 3-16) provides a summary of the medical NBC defense programs and the planned modernization strategy over the next fifteen years.

3.1.3 Reducing Reliance on Research Animals

The FY95 National Defense Authorization Act directed DoD to establish aggressive

programs to reduce, refine, or replace the use of research animals. In April 1995, DoD issued Directive 3216.1, "Use of Laboratory Animals in DoD Programs," which mandated standardization of all DoD animal use protocols. Therefore, an objective of the MCBRDRP is to utilize and develop technologies that will reduce reliance on animal research. In FY97, the MCBRDRP utilized computerized molecular modeling, computer predictions, *in vitro* cell cultures, a cell-free reaction system, and a lipid bilayer system to replace the use of animals when possible. All research proposals that use animals are evaluated by a statistician to ensure that only the minimum number of animals required to obtain scientific validity are used. Animals lower on the phylogenetic scale (or the least sentient species) are used if the selection will permit attainment of the scientific objective. Additionally, all procedures which would cause pain or distress in laboratory animals are reviewed by a veterinarian with expertise in laboratory animal medicine to determine the procedural modifications, analgesics and/or anesthetic regimens to be incorporated to minimize pain or distress.

It is the policy of DoD that animal utilization will be conducted in full compliance with the Animal Welfare Act and that animals are used in research only when scientifically acceptable alternatives are not available.

3.1.4 Medical Program Organization

Chemical/Biological. The U.S. Army is the Executive Agent for the MCBRDRP as prescribed in DoD Directive 5160.5 and, as such, is the lead requirements coordinator. The programs integrate DoD in-house and external efforts. Joint Technology Coordinating Group (JTCG) 3 (Medical CW Agent Defense) and JTCG 4 (Medical BW Agent Defense) of the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee are responsible for the programs' joint consolidation, coordination, and integration. The ASBREM Committee maximizes efficiency by coordinated planning, and minimizing unnecessary program overlaps and costly materiel retrofits. (The integration of program management and oversight of medical and non-medical NBC defense programs are described in Chapter 1.) The Army Technology Base Master Plan and the Medical Science and Technology Master Plan are the program drivers for the chemical and biological research programs. The science and technology base is managed through the development and execution of Defense Technology Objectives (DTO) and Army Science and Technology Objectives (STO). The predevelopment program (basic research; exploratory development; and concept exploration and definition) is directed by the U.S. Army Medical Research and Materiel Command (USAMRMC). The advanced development program (Program Definition and Risk Reduction [PDRR]); and Engineering and Manufacturing Development (EMD) for medical *chemical* defense products is directed by the U.S. Army Medical Materiel Development Activity (a USAMRMC asset). The advanced development program (PDRR and EMD) for medical *biological* defense products, including the joint vaccine acquisition program, is directed by the Joint Program Office for Biological Defense (JPO-BD).

Nuclear. The study of the medical and biological effects of ionizing nuclear radiation is performed by the tri-service Armed Forces Radiobiology Research Institute (AFRRI). AFRRI programs are integrated into other DoD in-house and external efforts under the coordination of

the ASBREM. Specific requirements and tasking for AFRRI research is not included in the funding or management structure of the DoD Chemical and Biological Defense program. A summary of AFRRI activities and accomplishments, however, are included in this chapter and in Annex D.

3.2 MEDICAL CHEMICAL DEFENSE RESEARCH PROGRAM

The mission of the Medical Chemical Defense Research Program (MCDRP) is to preserve combat effectiveness by timely provision of medical countermeasures in response to joint service chemical warfare defense requirements.

3.2.1 Goals

The goals of the MCDRP are:

- Maintain technological capabilities to meet present requirements and counter future threats:
  - Determine sites, mechanisms of action, and effects of exposure to chemical warfare agents with emphasis on exploitation of neuroscience technology and dermal pathophysiology.
  - Identify sites and biochemical mechanisms of action of medical countermeasures.
  - Exploit molecular biology and biotechnology to develop new approaches for medical countermeasures.
  - Exploit molecular modeling and quantitative structure-activity relationships supporting drug discovery and design.
- Provide individual prevention and protection to preserve fighting strength:
  - Develop improved prophylaxes, pretreatments, antidotes, and therapeutic countermeasures.
  - Develop skin protectants and decontaminants.
  - Identify factors that influence safety and efficacy properties of candidate countermeasures.
  - Develop and maintain preformulation, formulation, and radiolabeling capabilities.
- Provide medical management of chemical casualties to enhance survival, and expedite and maximize return to duty:
  - Develop concepts and recommend therapeutic regimens and procedures for the management of chemical casualties.
  - Develop diagnostic and prognostic indicators for chemical casualties.
  - Develop life-support equipment for definitive care.

3.2.2 Objectives

The objectives of the MCDRP differ with the varying threats:

- For vesicant (or blister) agents, the objective is to develop a pathophysiological database on vesicant chemical agents and develop a working hypothesis on how damage occurs at the cellular level. Used with associated technologies, this approach will enable the formulation of definitive pretreatment and treatment strategies and is expected to produce a realistic concept for medical prophylaxis, immediate post exposure therapy and topical protection.
- For nerve agents, the objectives are to field a safe and effective advanced anticonvulsant nerve agent antidote, and to field an advanced pretreatment based on biological scavengers, such as human enzyme butyrylcholinesterase (BuChE). Like acetylcholinesterase, the target enzyme for nerve agents, native BuChE is also inhibited by nerve agents. Through bioengineering efforts in the technology base, human BuChE has been mutated to a form that catalyzes the breakdown of nerve agent. The concept of using a catalytic BuChE to protect against large doses of nerve agent has been established in laboratory animals, indicating that this approach is feasible in humans. The enzyme pretreatment offers the potential advantage over the present pretreatment, pyridostigmine bromide (PB). The enzyme pretreatment affords long-term protection from a single dose rather than requiring three daily doses, as does PB.
- For blood agents, the objective is to develop and field a safe and effective cyanide pretreatment.
- For respiratory agents, the objective is to develop approaches to prophylaxis and therapy by understanding pathophysiological changes after agent exposure.

3.2.3 Threats, Countermeasures, Technical Barriers, and Accomplishments

The chemical warfare threats and countermeasures, as well as chemical defense research and development technical barriers and accomplishments, are outlined in Annex D (Section D.1).

3.3 MEDICAL BIOLOGICAL DEFENSE RESEARCH PROGRAM

The mission of the Medical Biological Defense Research Program (MBDRP) is to develop medical countermeasures to protect U.S. forces and thereby deter, constrain, and defeat the use of biological agents against them (DoD Directive 5160.5, May 1985). The program is directed against agents of biological origin that are validated military threats. A primary concern is the development of vaccines, drug therapies, diagnostic tools, and other medical products that are effective against agents of biological origin (see Table 3-1).

3.3.1 Goals

Goals of the MBDRP include the following:

- Protecting U.S. forces' war fighting capability during a biological attack.
- Reducing vulnerability to validated and novel threats by maintaining a strong technology base.
- Providing education on medical management of biological warfare casualties.

3.3.2 Objectives

In accomplishing the goals of the MBDRP, efforts are focused on three objectives:

- Prevent morbidity and mortality through the use of vaccines, drugs, and other medical pretreatments.
- Diagnose disease through the use of forward deployable diagnostic kits and confirmation assays.
- Treat casualties to maximize the number of warfighters that return to duty through the use of antitoxins, drugs, and other medical treatments.

The MBDRP responds to requirements from the DoD as identified in DoD Directive 6205.3, "Biological Defense Immunization Program," the Joint Service Agreement on Biological Defense, the Joint Warfighting Science and Technology (S&T) Plan, the Defense Technology Assessment Plan, and the Defense S&T Strategy.

Highly sophisticated technology base efforts for medical biological defense hold the promise of yielding important new products to protect our troops against a wide range of biological weapons. These products include multi-agent vaccines, which will reduce costs of vaccine production and simplify immunization schedules, and a common diagnostic kit, a hand-held device that can be deployed at forward sites to rapidly analyze clinical samples for the presence of biological warfare. The development of these products is also being supported by the Defense Advanced Research Projects Agency (see also section 3.3.4 below).

The measles-mumps-rubella (MMR) vaccine administered to children is an example of a licensed multi-agent vaccine. However, the technologies being explored for producing these new vaccines are more advanced, relying on bioengineering technologies such as naked DNA and the replicon-based delivery systems. In the naked DNA approach, DNA coding for protein antigens of the organism is injected with a "gene gun"; the DNA directs the synthesis of the antigens, which then stimulate the development of immunity. In the replicon approach, selected genes from biological warfare agents are introduced into an attenuated virus, which cannot produce disease. The virus directs the synthesis of the foreign proteins, inducing immunity. Research in both the naked DNA and replicon approaches is advancing rapidly, and transition of a multi-agent vaccine to advanced development is scheduled for FY 02.

Bioengineering techniques are also being used to prepare a variety of recombinant vaccines against single threat agents that will be produced without the need to grow the threat agent during the vaccine production process. Several recombinant vaccines are scheduled to be fielded over the next 10 years.

Development of a common diagnostic kit is proceeding with two state-of-the-art technologies. In the antibody based system, which is scheduled to be transitioned to advanced development in FY 99, a membrane platform will detect biological warfare threat agents in biological specimens. The second system relies on detecting the DNA of a variety of biological warfare threat agents or natural infectious diseases by a hand held polymerase chain reaction (PCR) technique and is scheduled to reach advanced development in FY 02. With these tools, clinical diagnoses will be made much faster (less than 30 minutes) and farther forward than is possible now.

The MBDRP includes the following areas of research:

- Bacterial studies – Identify virulence factors and protective antigens and the specific genes for these factors/antigens in bacterial threat agents. Determine the role of these factors in stimulating cellular and humoral immunity. Use this knowledge in the development of second generation recombinant vaccines. Evaluate modern antibiotics for effectiveness in the treatment and/or post-exposure prophylaxis of bacterial threat agents.
- Toxin research – Conduct basic and developmental research to discover methods of prevention and treatment against broad classes of toxins to include use of site-directed mutagenesis and protein engineering of recombinant vaccine candidates. Study mechanisms of action of high priority toxins in order to identify promising sites for drug intervention.
- Viral and Rickettsial studies – Identify and characterize threat organisms, conduct molecular antigenic analysis, and investigate pathogenesis, immunology, and epidemiology that will allow decisions regarding the optimal approach to disease prevention and control. Develop vaccine candidates and immunological and drug treatment strategies for viral and rickettsial threat agents.
- Diagnosis – Investigate and evaluate sensitive and specific methods for detection of infectious organisms, toxins, antigens and antibodies in biological materials including the application of nucleic acid probes or synthetic antigens. Develop rapid identification and diagnostic methods for the assay of toxins, metabolites, and analogs in clinical specimens.

3.3.3 Threats, Countermeasures, Technical Barriers, and Accomplishments

A biological threat agent is defined as an intentionally disseminated living microorganism or toxin that can cause disease or death in humans, animals, or plants. Threat agents include a broad range of microorganisms (bacteria, rickettsia, and viruses) and toxins of biological origin. Biological weapons are easy to make, difficult to detect and can be very effective. Defense against this class of weapon is difficult, particularly since biological agents can produce casualties for thousands of square kilometers. Biological agents can also be combined with nuclear, chemical, or conventional weapons and used with devastating effect.

Countermeasures and diagnostic techniques for biological weapons are shown in Table 3-1. Critical elements of medical biological defense include the ability to protect U.S. forces from BW agents, to rapidly diagnose (in biological specimens) infection or intoxication

from agents, and to treat casualties. Currently, the most effective countermeasure is pre-deployment active immunization. Future threats could involve genetically engineered biological weapons that may be easily produced, highly lethal, difficult to detect, and resistant to conventional therapies.[5]

The current MBDRP includes the following research areas for the development of medical countermeasures:

- Characterize the biochemistry, molecular biology, physiology, and morphology of biological warfare threat agents;
- Investigate the pathogenesis and immunology of the disease;
- Determine the mechanism of action of the threat agent in an animal model system;
- Select antigen(s) for candidate vaccines;
- Develop and compare potential vaccine candidates and characterize their effects in animal models;
- Establish safety and efficacy data for candidate vaccines;
- Develop medical diagnostics, including far forward, confirmatory, and reference lab;
- Develop chemo/immunotherapeutic agents and preparations.

Technical shortcomings in the private sector include the lack of high level biological containment (BL-3 and BL-4) laboratory facilities to support in-house biological defense research and scientific expertise in biological defense. This has become a critical issue in light of current personnel and program downsizing initiatives and the additional emphasis that is being placed on out-sourcing MBDRP work. The technological and scientific expertise for biological defense can therefore be eroded quickly.

Details of the biological warfare threats and countermeasures, as well as biological defense research and development technical barriers and accomplishments, are presented in Annex D (Section D.2).

[5] A detailed assessment of the potential impact of new or genetically engineered biological weapons is included in a report prepared by the Department of Defense entitled *Advances in Biotechnology and Genetic Engineering: Implications for the Development of New Biological Warfare Agents*. This report was submitted to Congress in June 1996.

Table 3-1. Medical Biological Defense Countermeasures and Diagnostic Techniques

VACCINES

- *Killed* – killed or inactivated microorganism that is incapable of replicating, yet stimulates immunity.
- *Live, attenuated* – live organism, genetically selected not to cause disease, yet able to stimulate immunity.
- *Toxoid* - toxin protein treated to inactivate its toxicity, yet retains its ability to stimulate immunity.
- *Recombinant* – gene coding for a protein that stimulates specific immunity to a BW agent is inserted into biological vector for production. Protein may be produced in high yields through bioengineering.
- *Deoxyribonucleic Acid (DNA)* – section of DNA that codes for protein that stimulates specific immunity to a BW agent. DNA produces the desired protein in recipient which stimulates immunity.
- *Polyvalent* – mixture of antigens that protect against a number of different BW agents.
- *Vectored* – carrier organism bioengineered to confer immunity against an unrelated BW agent or multiple agents.

ANTIBODY (ANTISERUM, ANTITOXIN)

- *Heterologous* – antibodies collected from animals (*i.e.*, different species than the recipient) repeatedly immunized against the BW threat. These antibodies must be treated to reduce the human immune response to them (serum sickness).
- *Homologous* – antibodies of human origin (*i.e.*, same species as the recipient) that provide protective immunity against the BW threat. These antibodies are not prone to stimulating serum sickness.
- *Monoclonal* – a cell culture technique for producing highly specific antibodies against a disease agent.
- *Bioengineered* – antigen binding site on the variable portion of an antibody elicited in a non-human system is combined with the non-variable portion of a human antibody to produce a "humanized" antibody.

DRUGS

- *Antibiotics* – very effective against bacteria, but are ineffective against viruses and toxins.
- *Others* – compounds that offer new possibilities for protecting against and treating exposure to BW agents (such as antiviral compounds).

DIAGNOSTIC TECHNOLOGIES

- *Immunological technologies* – tests relying on antibodies for detecting the presence of proteins associated with the BW agent. They are easy to use, compact, rapid (minutes), and require little logistic support. These tests are currently used in out-patient clinics and doctor's offices.
- *Nucleic acid technologies* – nucleic acid tests, specifically the polymerase chain reaction (PCR), rely on segments of genes unique to BW agents to detect the presence of those agents. These technologies are extremely sensitive and specific, but currently require more support to perform.

3.3.4 Defense Advanced Research Projects Agency (DARPA) Programs

As one of the major program areas conducted under its Defense Sciences Office, DARPA is pursuing the demonstration and development of new biological warfare defense capabilities. Major thrusts include medical countermeasures (developing barriers to prevent entry of pathogens into the human body, pathogen countermeasures to block pathogen virulence

and to modulate host immune response); a new emphasis in advanced medical diagnostics for the most virulent pathogens and their molecular mechanisms; and consequence management tools.

Medical countermeasures to be developed include: (1) multi-agent therapeutics against known, specific agents, and (2) therapeutics against virulence pathways (mechanisms of disease) shared by broad classes of pathogens. Specific approaches include modified red blood cells to sequester and destroy pathogens, modified stem cells to detect pathogens and to induce immunity or produce appropriate therapeutics within the body, identification of virulence mechanisms shared by pathogens, development of novel therapeutics targeting these mechanisms, and efficacy testing in cell cultures and animals.

Early diagnosis is key to providing effective therapy against BW agents since many of these agents cause early nonspecific flu-like symptoms. The ultimate goal of the DARPA advanced medical diagnostics thrust is to develop the capability to detect the presence of infection by biological threat agents, differentiate from other significant pathogens, and identify the pathogen, even in the absence of recognizable signs and symptoms (when the pathogen numbers are low).

Mission effectiveness requires rapid, correct medical responses to biological weapon threats. The objective of the consequence management thrust is to provide comprehensive protocols to protect or treat combatants using current and emerging biological countermeasures. It will provide accelerated situational awareness for biological warfare events by detecting exposure to agents through an analysis of casualty electronic theater medical records, and will locate and determine the most effective logistical support for providing appropriate treatment and pathogen-specific resources required to mitigate effects of the attack. Current plans envision transitioning these software tools to service customers beginning in FY 99.

3.4 MEDICAL NUCLEAR (RADIOLOGICAL) DEFENSE RESEARCH PROGRAM

The mission of the Medical Nuclear Defense Research Program (MNDRP) is to conduct research in the field of radiobiology and related matters essential to the support of the Department of Defense and the Military Services. The sole repository of defense radiobiology research expertise is AFRRI.

3.4.1 Goals

The goals of the MNDRP are the following:

- Develop medical countermeasures for the acute, delayed and chronic effects of radiation.
- Identify and quantify hazards of depleted uranium munitions to military and civilian casualties, both female and male.
- Develop rapid bioassay for radiation injury suitable for field deployment
- Produce improved chelating agents for use in treating internal contamination by radioactive heavy metals.

- Sustain combat capability, increase survival, and minimize short- and long-term health problems associated with ionizing radiation alone, and when radiation is combined with other weapons of mass destruction.
- Respond to immediate operational requirements that obligate expertise in either radiation medicine, health physics or radiobiology.
- Maintain core of scientific expertise necessary to meet current research requirements and to counter current and future radiological threats.
- Provide nuclear radiation weapon effects medical training for DoD medical personnel.

3.4.2 Objectives

The primary objective of this research group is to address the major aspects of military operational requirements for dealing with radiation injuries. A nuclear threat agent is any weapon which causes detrimental medical effects by either direct external irradiation or by internal contamination with radioactive material. These agents include radiation dispersal weapons, which scatter radioactive material with conventional explosives, deliberate area contamination, destruction of a nuclear power plant, improvised nuclear devices, and traditional nuclear weapons. Operational requirements include programs in casualty management, medical radioprotectants to diminish radiation injury, medical therapeutic regimens, maintenance of performance, and radiation hazards assessment.

3.4.3 Threats, Countermeasures, Technical Barriers, and Accomplishments

The deployment of a relatively low-yield nuclear device or Hiroshima-type weapon is increasingly possible by a terrorist or third-world country. Such a device could be utilized against either a military installation or a political target (e.g., the seat of government, large population center, or commercial port city). In such a scenario, citizens outside the immediate lethal area could be exposed to the prompt radiation of the initial explosion as well as to chronic exposures resulting from the residual radioactive fallout.

Early radiation injury diminishes the soldier's ability to fight and survive. Effective radiation countermeasures must protect the soldier from performance decrement and simultaneously diminish lethality and the long-term effects of radiation injury. Therapeutic measures will increase the survival and diminish the morbidity of individual soldiers who are wounded by radiation. A research program to understand molecular and cellular damage induced by radiation is needed to determine the best medical countermeasures for new radiogenic wounding agents on the modern battlefield. Table 3-2 presents an overview of various medical approaches to prevent or counter the various threats of radiological exposure. Program accomplishments are detailed in Annex D.

Table 3-2. Medical Nuclear Defense Countermeasures

PRETREATMENTS

Multidrug combinations: Animal research has demonstrated certain radioprotectant drug combinations administered at nontoxic levels interact synergistically to markedly increase mammalian resistance to radiation.

Antiemetics: Granisitron (KytrilR) has been adopted as the NATO standard pretreatment antiemetic medication to significantly block performance degrading early symptoms of radiation injury. This allows mission completion and consequently diminishes the overall casualty rate.

DEPLETED URANIUM TOXICITY

Metabolism of metallic uranium fragments: Prior to the wounding of soldiers in Desert Storm, very little was known about the toxicity of implanted metallic uranium fragments. Previous uranium toxicity studies had been limited to inhaled uranium oxides in uranium workers. Preliminary aspects of animal studies indicate distribution to depot sites throughout the body and potential risks of late effects. Adequate chelation therapy does not exist at this time to increase excretion of this material.

Fetal metabolism of depleted uranium: Young female soldiers may be wounded by depleted uranium weapons. No knowledge exists of the effects of this material on subsequent pregnancies.

MEDICAL THERAPIES

Specific Cell Line Stimulants: Granulocyte-Macrophage Colony Stimulating Factor has been demonstrated to be highly effective in restoring the immune competence of bone marrow and allowing survival from radiation injuries previously considered lethal. The cytokine thrombopoietin has been developed as a therapeutic agent and is undergoing further trials as a platelet-formation stimulant.

Broad Range Cellular Recovery Stimulants: Research continues into biologically stable compounds which stimulate recovery of multiple hematopoietic cell lines.

Susceptibility to Infectious Agents and Efficacious Therapy: Research continues to assess susceptibility and resistance to infectious agents in conjunction with use of prompt and chronic sublethal irradiation, and to develop combined modality therapies that attack microorganisms and enhance innate immune response in irradiated personnel.

Internal Contamination Chelation Agents: Currently available chelation agents capable of removing internal radioisotopes are investigational drugs which have been utilized with limited success. More effective ligand-type compounds have been identified and are undergoing evaluation. Other modalities being investigated include seaweed based Alginates, which appear to be promising.

DIAGNOSTIC TECHNIQUES

Biodosimetry and Dose Assessment: No dose assessment method, other than individual physical dosimeters can be currently made available to deployed soldiers. Automated chromosome dicentromeric analysis has been developed and can be made deployable to the Echelon 3 medical care level. Other, more rapid, methods are being evaluated.

CHEMICAL AND BIOLOGICAL WARFARE INTERACTIONS WITH RADIATION

Increased lethality of biological weapons after low level irradiation: Ongoing studies indicate even low levels of radiation exposure will markedly increase the infectivity of biological weapons. Existing data suggest synergistic interactions of mustard and nerve agents with ionizing radiation.

Significant progress has been made in prophylactic and therapeutic measures that will reduce mortality and morbidity in high dose radiation environments. During the Cold War, the numbers of casualties resulting from the large scale deployment of nuclear weapons would have easily overwhelmed the medical assets of NATO forces. In the current threat environment, adequate planning for medical response to a very limited nuclear attack is mandatory. While casualty numbers from a nuclear detonation will still be large, countermeasures have been developed which will significantly limit the morbidity and the secondary mortality. These modalities will be particularly important in the likely scenario of terrorist use of radiation weapons. If the attack is limited to one or, at worst, a small number of events, the ability to provide intensive, sophisticated medical and other support is highly credible because of the availability of uncompromised treatment/research centers and medical evacuation capabilities.

Details of the radiological threats and countermeasures, as well as nuclear defense research and development technical barriers and accomplishments, are presented in Annex D (Section D.3).

3.5 MEDICAL NBC RESEARCH PROJECTION

Table 3-3 presents a projection of the medical NBC defense programs and modernization strategy for the next 15 years.

Table 3-3. Medical NBC Defense Programs and Modernization Strategy

	NEAR (FY98-00)	MID (FY01-05)	FAR (FY06-12)
Medical - Chemical Defense	**Licensed Topical Skin Protectant**	**Licensed Advanced Anticonvulsant** **Licensed Cyanide Pretreatment** **Licensed Multi-chambered Autoinjector**	**Licensed Reactive Topical Skin Protectant** **Licensed Advanced Prophylaxis for Chemical Warfare Agents** **Licensed Specific Protection and Treatment for Blister Agents (vesicant agent countermeasures)** **Licensed Vesicant Agent Prophylaxis**
Medical - Biological Defense	**Anthrax vaccine Relicensure**	**Licensed Q fever chloroform-methanol residue (CMR) vaccine** **Licensed Tularemia vaccine** **Licensed Vaccinia, cell culture derived vaccine** **Licensed Botulinum A/B/E/F monovalent vaccines** **Rapid Diagnostic Kit for Biological Warfare Threat Agents** **Licensed Botulinum Tetravalent vaccine** **Licensed Botulinum C vaccine** **Licensed Botulinum D vaccine** **Licensed Botulinum G vaccine** **Licensed Ricin vaccine** **Licensed Brucellosis vaccine** **Licensed new Anthrax vaccine**	**Licensed Staphylococcal Enterotoxin B (SEB) vaccine** **Licensed new Plague vaccine** **Licensed new Venezuelan Equine Encephalomyelitis (VEE) vaccine** **Licensed combined VEE, Western Equine Encephalomyelitis (WEE), & Eastern Equine Encephalomyelitis (EEE) vaccine** **Multi Agent vaccine delivery system** **Hand Held Common Diagnostic System**
Medical - Nuclear Defense	**Depleted uranium fragments toxicity assessment** **Evaluation of new chelation agents (ligands and Alginates)** **Multidrug radioprotectants validated** **Combination cytokine therapy validated** **Echelon 3 fieldable biodosimetry** **Licensed novel drug-delivery systems** **Risk Assessment for low-dose, low-dose rate radiation effect**	**Licensed treatment modalities for depleted uranium fragments casualties** **Radioprotectant transdermal patches** **New generation prophylactic and therapeutic immunomodulators for multi-organ injuries** **Computer models to understand effects resulting from combined NBC attacks**	**Licensed Radiation-induced cancer/mutation preventive techniques** **Licensed Countermeasure for Chem-Bio-Radiation interaction**

3.6 MEDICAL R&D REQUIREMENTS ASSESSMENT

ISSUE: **DoD lacks FDA licensed vaccines against BW threat agents.**

SOLUTION: DoD has established a prime systems contract for the Joint Vaccine Acquisition Program. The program establishes a single entity to develop, procure, and stockpile vaccines for protection against BW agents. The contractor will be required to obtain and maintain FDA licensure and will also be responsible for clinical trials.

The prime systems contract was awarded in November 1997 and begins with a base contract for the licensure of three Biological Defense vaccine products: Q fever, Tularemia, and Vaccinia, and the storage of the current contingency BD vaccine stockpile (IND products). There are options for the development and licensure of fifteen other BD vaccines, with production options for all eighteen. The period of performance for this contract is ten (10) years.

ISSUE: **Anthrax vaccine issues. Anthrax vaccination currently requires a primary series, six dose regimen spaced out over the course of 18 months, with an annual booster to maintain immunity. The timetable for the vaccination series makes it difficult to complete before deployment of forces or to ensure that mobile forces, once deployed, are administered the proper regimen.**

SOLUTION: On December 15, 1997, the Secretary of Defense announced the decision to systematically vaccinate all U.S. military personnel against anthrax. Vaccinations would start only after the following conditions are met:

- Supplemental testing be performed, consistent with FDA standards, to assure sterility, potency, and purity of the vaccine
- Implementation of a system for fully tracking personnel who receive the vaccinations
- Approval of operational plans to administer the immunizations and communications plans to inform military personnel of the program
- Review of health and medical issues of the program by an independent expert.

Current plans call for personnel serving in high threat regions to receive vaccinations beginning in summer 1998. Total force vaccination will follow according to a schedule to be developed. This decision is crucial for developing a strategy to maintain the industrial base capability for vaccine production.

Currently, the sole FDA-licensed producer of anthrax vaccine for DoD is Michigan Biologic Products Institute (MBPI) in East Lansing, Michigan. The State of Michigan plans to divest itself from MBPI by February 18, 1998. The State intends to privatize the facility, and some commercial companies have expressed interest. (MBPI produces other medical products in addition to anthrax vaccine.) A condition of the sale includes

conveying current DoD contracts to the new owner.

However, a recent FDA audit found MBPI deficient in some areas of regulatory compliance, jeopardizing its FDA-licensure. Due to the evolution of stringent regulations, licensure of a new facility for anthrax vaccine production would delay the program prohibitively. Therefore, JPO-BD worked with the manufacturer to develop a strategic plan that would ensure its continued capability to produce anthrax vaccine and to maintain FDA licensure.

ISSUE: **The effects on humans resulting from exposure to low doses of chemical agents, particularly organophosphate (nerve) agents, are not clearly understood.**

SOLUTION: Beginning in FY96, DoD, in association with the Research Working Group of the Interagency Persian Gulf Veterans' Coordinating Board, dedicated $5 million to evaluate the chronic effects of low-dose level exposure to chemical agents. Studies have been under way since 1QFY97 to develop highly specific and sensitive assays, preferably forward deployable, to detect, and potentially quantify, low-level exposure to chemical agents. These ongoing studies may also identify any long-lasting and toxic metabolites of chemical agents which could account for delayed and long-term health consequences. In addition, studies to look at the impact of possible genetic polymorphisms of cholinesterase enzymes upon individual response to nerve agents are under way. Additional funds have been committed and contracts are being awarded to evaluate potential chronic health complaints resulting from exposure to nerve agents. These contracts will begin in 1QFY98.

ISSUE: **Radiation exposures below a level that causes acute effects predispose military personnel to injury from other battlefield agents. The magnitude of this interaction has not been fully evaluated.**

SOLUTION: Definitive assessment of NBC threat interactions and NBC agent modeling will support the strategic design and development of specific preventative and treatment countermeasures.

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